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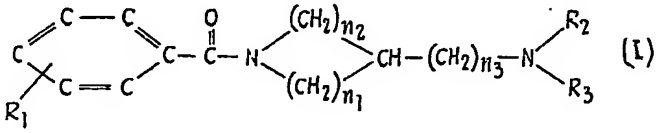
(54) PIPERIDINE COMPOUNDS FOR THE TREATMENT OF PARKINSONISM

(71) We, LØVENS KEMISKE FABRIK PRODUKTIONSAKTIESELSKAB, a Company, inporated under the Laws of Denmark, of Ballerup, Denmark, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a series of hitherto unknown compounds of the general formula:



(I)

wherein R_1 is a straight or branched C3 to C12 aliphatic hydrocarbon chain, unsubstituted or substituted with phenyl, phenoxy or phentylthio, which R_1 is directly attached to the benzene nucleus, or optionally may be attached to the benzene nucleus through a hetero atom which is an oxygen or sulphur atom; R_2 is alkyl, R_3 is a cycloalkyl radical with from 5 to 8 carbon atoms in the ring, and R_2 together with R_3 and the nitrogen atom can complete a heterocyclic ring which may be alkyl-substituted, n_1 is an integer from 2 to 4, n_2 is an integer from 1 to 5, and n_3 is an integer from 1 to 3; to salts of the compounds with pharmaceutically acceptable inorganic and organic acids; and to methods for the preparation of the compounds and their salts.

When ever used in the statement above or in the description below, the term "alkyl" means lower-alkyl, including straight and branched aliphatic hydrocarbon chains with from 1 to 6 carbon atoms in the chain.

The compounds of the invention possess valuable pharmacological activities, thus e.g. they display a favourable central anticholinergic action and are intended to be used in the treatment of patients suffering for instance from parkinsonism, including the post-encephalytic or arteriosclerotic parkinsonism and similar conditions.

As implied in the term, post-encephalytic parkinsonism refers to the appearance as a sequence to encephalitis of muscle rigidity and tremor frequently along with spasmodic phenomena, whereas the term arteriosclerotic parkinsonism refers to the appearance as a consequence of multiple cerebral vascular lesions of difficulties of movements and fixity of posture, and similar conditions occurring in the older age group, often combined with muscle rigidity while tremor is absent. The said disorders are chronic and progressive and consequently all treatment is symptomatic and must be continued for long periods of time.

The medication may comprise treatment with belladonna alkaloids, e.g. atropine,

amphetamine alone or in combination with belladonna alkaloids, with certain antihistaminics or apomorphine, and similar unspecific medications, which may offer some degree of symptomatic relief on tremor or spasmotic conditions, but no fixed dosage can be recommended and ordinarily small amounts of the drug in question are used initially while larger doses are ultimately required whereby it may be necessary to approach the limit of tolerance and several toxic symptoms appear. Better results in the treatment of parkinsonism have been observed by using certain synthetic drugs as e.g. trihexaphenidyl (3 - (1 - piperidyl) - 1 - phenyl - 1 - cyclohexyl - 1 - propanol), Caramiphen (2 - diethylaminoethyl - 1 - phenyl - cyclopentane - 1 - carboxylate hydrochloride), or Diethazide (diethylaminoethyl - N - dibenzoparathiazine).

The action of trihexyphenidyl resembles that of atropine, in particular as far as the antispasmotic properties are concerned whereas some of the undesired effects of atropine are weaker, but still the peripheral parasympatholytic action of trihexyphenidyl must be considered an undesired effect in the treatment of parkinsonism where in particular the central action is important.

As far as the chemical constitution is concerned the compounds of the present invention differ far from the drugs mentioned above, and it has surprisingly been found that the compounds of formula I exert a favourable specific therapeutic action with a view to the treatment of all forms of parkinsonism.

According to experiments the preferred compounds with a view to treatment of parkinsonism are those of formula I in which R_1 is a C5 to C7 aliphatic hydrocarbon chain attached to the benzene nucleus through the hetero atoms O or S, in which the integers n_1 and n_2 are within the limits from 2 to 3, and from 2 to 4 respectively, and in which R_2 is a C1 to C2 aliphatic alkyl group, and R_3 is a C4 to C7 cycloalkyl group, or in which R_2 and R_3 together with the N atom form a heterocyclic ring.

In particular, however, the preferred compounds are those in which R_1 has the meaning defined above and are in the 4-position in the benzene nucleus, and in which R_2 and R_3 together form an unsubstituted or alkyl-substituted pyrrolidino, piperidino, hexamethyleneimino or heptamethyleneimino group.

Thus the compound 1 - (4 - n - hexyloxybenzoyl) - 4 - (piperidinoethyl) - piperidine hydrochloride, among a series of related compounds, displayed a promising central anticholinergic activity, while its peripheral parasympatholytic effects were comparably weak. Its antagonistic effects against the tremorgenic action of tremorine and oxotremorine, which is considered to be the most predictive pharmacological model of parkinsonism, were two to five times stronger than those of trihexyphenidyl being at present the drug of choice in the treatment of parkinsonism. Furthermore, the central effects of oxotremorine (tremor) were inhibited with lower doses than the peripheral effects (salivation) which as mentioned above is highly desirable for antiparkinsonism drugs.

Experiments in higher animals further confirmed the favourable weak peripheral anticholinergic action of the compounds of the invention.

The acute oral toxicity of e.g. 1 - (4 - n - hexyloxybenzoyl) - 4 - (piperidinoethyl) - piperidine HCl expressed in LD_{50} (mice) is 470 mg/kg. which may be considered low when compared to the degree of activity in the anti-parkinson test in which an effect could be observed with amounts of the order 0.5 to 2.0 mg/kg..

The chronic toxicity was studied in animal experiments in which the test animals were rats (Leo Wistar strain). The compounds were administered orally each day in a period of six months in various doses, in one animal section in a daily dose of 50 mg/kg..

Even in this latter section no adverse clinical signs were seen and no adverse changes in bodyweight could be demonstrated. The investigation comprises a full haematological and pharmacological analysis of the animals and after post-mortem examinations no abnormalities were demonstrated.

A pharmaceutical composition containing a compound of the invention also constitutes part of this invention. In the composition, the proportion of therapeutically active material to carrier substances and auxiliary agents can vary between 0.04 to 10%, depending upon the form of pharmaceutical presentation.

The composition in question can be worked up to pharmaceutical forms of presentations such as tablets, pills, dragees and suppositories, or the composition can be filled in medical containers such as capsules or ampoules or, as far as mixtures or elixirs are concerned, they may be filled in bottles and similar containers.

Pharmaceutical inorganic or organic, solid or liquid carriers suitable for enteral and paranteral administration can be used to make up the composition; water, gelatine, lactose, starch, magnesium stearate, talc, vegetable and animal oils and fats, benzyl alcohol, gum, polyalkylene glycol and similar other known carriers for medicaments are suitable as carriers while stabilizing agents, wetting or emulsifying agents, salts for varying the osmotic pressure or buffers for securing an adequate pH-value of the composition can be used as auxiliary agents.

In the composition, the compounds of for-

mula I may be present as such or in the form of one of their salts with a pharmaceutically acceptable inorganic or organic acid as for instance a hydrochloride, hydrobromide, hydroiodide, sulphonate, sulphate, phosphate, sulphamate, tartrate, malate, citrate, acetate, succinate or benzoate.

Another object of the invention resides in the selection of a dose of the compounds of formula I which can be administered so that the desired activity is achieved without simultaneous secondary effects.

The compounds of the invention may in clinical practice conveniently be administered by injection, preferably once per day and in amounts corresponding to a total daily dose of from 0.1 to 25 mg.

In particular, however, the compounds may be given by the oral route in the form of tablets or capsules, or in the form of a mixture or elixir, one to four times per day and in a total daily dose of from 0.2 to 50 mg., always with due regard to the condition of the patient and in accordance with the prescription of the medical practitioner.

The compounds of the invention may conveniently be administered in dosage units containing not less than 0.5 mg., and preferably from 1 to 25 mg. of the active compound.

By the term "dosage unit" is meant a unitary, i.e. a single dose capable of being administered to the patients, and which may be readily handled and packed remaining as a physically stable unit dose comprising either the active material as such or as a mixture of it with solid or liquid pharmaceutical diluents or carriers.

If the compound is to be injected, a sealed ampoule, a vial or a similar container may be provided containing a parenterally acceptable aqueous or oily injectable solution or dispersion of the active material as a dosage unit mentioned above.

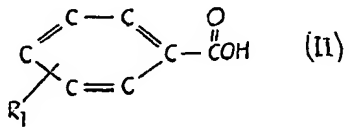
When in the form of tablets, pills or capsules, the dosage unit may contain from 0.5 to 25 mg. and preferably contains from 1 to 10 mg. of the active compound which is readily absorbed when orally administered.

When in the form of an injectable preparation the dosage unit preferably contains from 0.1 to 25 mg. of the active compound.

When the active compound is administered as a mixture or elixir, this pharmaceutical preparation may preferably contain 0.5 to 10 mg. per cc. The dosage units aforesaid also constitute part of the present invention.

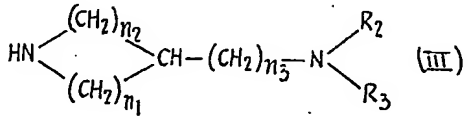
It is still another object of the invention to provide a method of producing the compounds represented by the general formula I.

In the method of the invention, an acid of the general formula:



(II)

wherein R_1 has the meaning hereinbefore defined is reacted in the form of an acid halide, on anhydride, a mixed anhydride with an alkyl-carbonic acid, a carboxylic acid, a sulphonic acid or with an inorganic acid, or in the form of a reaction derivative obtained by reacting the acid with a carbodiimide or N',N' - carboxyldiimidazole, with a compound of the general formula:



(III)

wherein R_2, R_3, n_1, n_2 and n_3 have the meanings hereinbefore defined, whereafter the compound formed is recovered as such or as one of its salts with an acid.

Most of the starting substances of formulae (II) and (III) are known compounds the preparation of which is described in the literature, or they may, if not known, be prepared in analogy with the known compounds.

Thus e.g. certain functional reactive derivatives of the alkylthiobenzoic acids used as starting substances in the method are hitherto unknown compounds which may be prepared in a Sandmeyer reaction in which the diazotized *m*- or *p*-aminobenzoic acid is reacted with an alkalimetal xanthogenate to form the corresponding xanthate, which in one step is hydrolyzed and alkylated by reacting with an alkylhalide under alkaline conditions resulting in the desired alkylthiobenzoic acid.

As indicated the acid of formula (II) is used in the form of one of its reactive derivatives as for instance an acid halide, such as an acid chloride or bromide, an anhydride, a mixed anhydride with an alkyl-carbonic acid, such as isobutyl-carbonic acid, a carboxylic acid, an inorganic acid or a sulphonic acid; or a derivative obtained by reacting the corresponding free acid with a carbodiimide or N',N' - carbonyldiimidazole.

The process of the invention is conveniently performed in the presence of an inert solvent and in the absence of water at room temperature for a period of time necessary to accomplish the desired degree of conversion, commonly by standing overnight. In this embodiment equimolar amounts or an excess

of the compound of formula (II) may appropriately be employed in order to form e.g. the hydrogen halide of compounds of formula (I) directly in the reaction mixture.

In another embodiment the reaction is performed in the presence of an inert solvent, preferably immiscible with water, and at temperatures at or below 0° C. while the acid component possibly formed during the reaction e.g. a hydrogen halide, is continuously removed by adding an aqueous solution of a base, e.g. an alkali metal hydroxide. In this embodiment the starting substances are used in equivalent amounts, or substantially in equivalent amounts, and the reaction may be completed within a few hours.

After complete reaction, the desired compound is readily recovered from the organic phase, if necessary after having removed a possible excess of starting substance of formula (II) by extraction with an aqueous solution of an inorganic base, by evaporation of the organic phase, and recrystallizating the residue, or the compound may be isolated as a salt with an acid by neutralizing the base, in a suitable solvent or mixture of solvents with a view to the precipitation or crystallization of the salt.

The invention will now be illustrated by the following non-limiting Examples, of which Examples 1 to 4 illustrate the preparation of intermediates and Examples 5 to 8, illustrate the preparation of the compounds of formula (I):—

EXAMPLE 1

4-n-Hexylthiobenzoic acid

To a solution of 4 - aminobenzoic acid (32 g.), sodium nitrite (18.8 g.) and sodium hydroxide (11 g.) in water (150 ml.) concentrated hydrochloric acid (50 ml.) was slowly added while stirring rigorously at −5—0° C. After the addition was completed the stirring was continued for a further 1 hour at 0—5° C. The cooled diazonium-solution was filtered and slowly added to a solution of potassium xanthogenate (62.5 g.) and sodium carbonate (87.5 g.) in water (250 ml.) while stirring vigorously at 65—70° C. The mixture was stirred at 65—70° C. for a further 1 hour. After cooling the mixture was carefully acidified with concentrated hydrochloric acid (150 ml.). The precipitated material was filtered off, washed with water and dissolved in 10% sodium hydroxide solution (500 ml.). The flask was filled with nitrogen, closed and left overnight. n-Hexylbromide (85 g.) was added and the mixture was refluxed for 3 hours. The resulting mixture was poured into concentrated hydrochloric acid (200 ml.)/ice (about 200 g.), and the precipitate was filtered off and washed with water. After drying, 22 g. of crude 4-n-hexylthiobenzoic acid with a melting point of 89—93° C. was obtained. A sample repeatedly recrystallized from cyclohexane had a melting point of 96—98° C.

EXAMPLE 2

4 - (4 - Phenylbutoxy) - benzoic acid

A solution of ethyl 4-hydroxy benzoate (11 g.), 4 - phenylbutylbromide (17 g.) and sodium (1.53 g.) in ethanol (50 ml.) was refluxed for 20 hours and was then evaporated *in vacuo*. 4 N sodium hydroxide (25 ml.) was added to the residue, and the mixture was heated on a steam bath for 5 hours. After cooling the resulting solution was acidified with concentrated hydrochloric acid (15 ml.). The precipitated material was collected by filtration and washed with water. After drying, 4 - (4 - phenylbutoxy) - benzoic acid with a melting point of 128—131° C. was obtained. Recrystallization twice from aqueous ethanol raised the melting point to 130—132° C. By substituting in the above procedure equimolar amounts of 2 - n - butylthioethylchloride for the 4 - phenylbutylbromide, 4 - (2 - n - butylthioethoxy) - benzoic acid (m.p. 95—97° C.), was obtained.

EXAMPLE 3

4 - Piperidinomethyl - piperidine dihydrochloride hydrate

To a stirred mixture of piperidine (12 g.), potassium carbonate (28 g.) and methanol (100 ml.), 4 - chloromethylpyridine hydrochloride (16.4 g.) was added in portions. The mixture was stirred at room temperature for a further 2 hours and was then evaporated *in vacuo*. The residue was treated with 2 N sodium hydroxide (25 ml.) and the separated oil was extracted with diethyl ether. The organic phase was dried ($MgSo_4$) and distilled. 4 - Piperidinomethylpyridine with a boiling point of 126—126.5° C. at 9 mm. Hg. was obtained. This material was dissolved in a mixture of methanol (75 ml.) and 3 N hydrochloric acid (45 ml.) and was hydrogenated after addition of PtO_2 (0.5 g.). The hydrogen uptake was complete within 3.5 hours. The catalyst was removed by filtration and the filtrate was evaporated *in vacuo*. The crystalline residue was triturated with acetone and collected by filtration. After drying, 4 - piperidinomethylpiperidine dihydrochloride hydrate with a melting point of about 260° C. was obtained. Recrystallization from ethanol raised the melting point to 265—266° C.

EXAMPLE 4

4 - [2 - (4 - Methylpiperidino) - ethyl] - piperidine dihydrochloride

A mixture of 4-vinylpyridine (25 g.), 4 - methylpiperidine (35.4 g.) and acetic acid (3.5 ml.) was heated on a steam bath for 24 hours. 4 N Sodium hydroxide (25 ml.) was added to the cooled mixture and the separated oil was extracted with diethyl ether.

The organic phase was dried ($MgSo_4$) and distilled. 4 - [2 - (4 - methylpiperidino) - ethyl] - pyridine with a boiling point of 151—154° C. at 9 mm. Hg. was obtained. This material was dissolved in a mixture of methanol (230 ml.) and 4 N hydrochloric acid (130 ml.) and was hydrogenated after addition of PtO_2 (1.0 g.). The hydrogen uptake was complete within 20 hours. The catalyst was removed by filtration and the filtrate was evaporated *in vacuo*. The crystalline residue was triturated with acetone and was collected by filtration. After drying, 4 - [2 - (4 - methylpiperidino) - ethyl] - piperidine dihydrochloride with a melting point higher than 290° C. was obtained. By substituting in the above procedure equimolar amounts of 3 - methylpiperidine or N-methylcyclohexylamine for the 4 - methylpiperidine, 4 - [2 - (3 - methylpiperidino) - ethyl] - piperidine dihydrochloride (m.p. 267—269° C.) and 4 - (2 - N - methylcyclohexylaminoethyl) - piperidine dihydrochloride (hygroscopic) were obtained respectively.

Example 5

1 - (4 - n - Hexyloxybenzoyl) - 4 - (2 - piperidinoethyl) - piperidine hydrochloride

A solution of 4 - n - hexyloxybenzoyl chloride (5.0 g.) in methylenechloride (25 ml.) was slowly added to a mixture of 4 - (2 - piperidinoethyl) piperidine dihydrochloride (5.4 g.), methylenechloride (25 ml.) and 2 N sodium hydroxide (50 ml.) while stirring at 0—5° C. After the addition was complete the stirring was continued for a further 4 hours. The organic layer was separated, washed with brine, dried ($MgSO_4$) and evaporated *in vacuo*. The remaining material was dissolved in diethylether (50 ml.) and acidified with dry ethanolic hydrochloric acid. The precipitated oily material was crystallized from isopropanol/diethylether. After drying and recrystallization from acetone, 6.3 g. of 1 - (4 - n - hexyloxybenzoyl) - 4 - (2 - piperidinoethyl) - piperidine hydrochloride with a melting point of 197.5—198.5° C was obtained.

Example 6

By substituting in the above procedure equimolar amounts of 4 - n - propyloxybenzoyl chloride, 4 - isopropyloxybenzoyl chloride, 4 - n - butyloxybenzoyl chloride, 4 - sec - butyloxybenzoyl chloride, 4 - isobutyloxybenozyl chloride, 4 - isoamyloxybenzoyl chloride, 4 - n - heptyloxybenzoyl chloride, 4 - n - octyloxybenozyl chloride, 3 - n - propyloxybenzoyl chloride, 3 - n - butyloxybenzoyl chloride, 3 - n - amyloxybenzoyl chloride, 3 - n - hexyloxybenzoyl chloride, 4 - n - hexylthiobenzoyl chloride, 4 - n - butylbenzoyl chloride, 4 - n - pentylbenzoyl chloride, 4 - n - hexylbenzoyl chloride, 4 - (2 - phenylethoxy) - benozyl chloride, 4 - (3 - phenylpropoxy) - benzoyl chloride, 4 - (4 - phenyl butoxy) - benzoyl chloride, 4 - (2 - phenoxyethoxy) - benzoyl chloride, 4 - (2 - n - butylthioethoxy) - benzoyl chloride, 4 - n - heptylbenzoyl chloride, or 4 - n - octylbenzoyl chloride, for the 4 - n - hexyloxybenzoyl chloride, 1 - (4 - n - propyloxybenzoyl) - 4 - (2 - piperidinoethyl) - piperidine hydrochloride (m.p. 192—193.5° C.), 1 - (4 - isopropyloxybenzoyl) - 4 - (2 - piperidinoethyl) - piperidine hydrochloride (m.p. 218—220° C.), 1 - (4 - n - butyloxybenzoyl) - 4 - (2 - piperidinoethyl) - piperidine hydrochloride, (m.p. 194.5—195.5° C.), 1 - (4 - sec.butyloxybenzoyl) - 4 - (2 - piperidinoethyl) - piperidine hydrochloride (m.p. 172—174° C.), 1 - (4 - isobutyloxybenzoyl) - 4 - (2 - piperidinoethyl) - piperidine hydrochloride (m.p. 189—191° C.), 1 - (4 - isoamyloxybenzoyl) - 4 - (2 - piperidinoethyl) - piperidine hydrochloride (m.p. 207—209° C.), 1 - (4 - n - heptyloxybenzoyl) - 4 - (2 - piperidinoethyl) - piperidine hydrochloride (m.p. 197—199° C.), 1 - (4 - n - octyloxybenzoyl) - 4 - (2 - piperidinoethyl) - piperidine hydrochloride (m.p. 198.5—199.5° C.), 1 - (3 - n - propyloxybenzoyl) - 4 - (2 - piperidinoethyl) - piperidine hydrochloride semihydrate (m.p. 156.5—158.5° C.), 1 - (3 - n - butyloxybenzoyl) - 4 - (2 - piperidinoethyl) - piperidine hydrochloride (m.p. 135.5—136.5° C.), 1 - (3 - n - amyloxybenzoyl) - 4 - (2 - piperidinoethyl) - piperidine hydrochloride (m.p. 124—126° C.), 1 - (3 - n - hexyloxybenzoyl) - 4 - (2 - piperidinoethyl) - piperidine hydrochloride (m.p. 135—136° C.), 1 - (4 - n - hexylthiobenzoyl) - 4 - (2 - piperidinoethyl) - piperidine hydrochloride (m.p. 166—168° C.), 1 - (4 - n - butylbenzoyl) - 4 - (2 - piperidinoethyl) - piperidine hydrochloride (m.p. 171.5—172.5° C.), 1 - (4 - n - pentylbenzoyl) - 4 - (2 - piperidinoethyl) - piperidine hydrochloride (m.p. 170.5—172° C.), 1 - (4 - n - hexylbenzoyl) - 4 - (2 - piperidinoethyl) - piperidine hydrochloride (m.p. 172.5—173.5° C.),

1 - [4 - (2 - phenylethyl) - benzoyl] - 4 - (2 - piperidinoethyl) - piperidine hydrochloride (m.p. 190—101.5° C.), 1 - [4 - (3 - phenyl propoxy) - benzoyl] - 4 - (2 - piperidinoethyl) - piperidine hydrochloride (m.p. 204—205° C.), 1 - [4 - (4 - phenylbutoxy) - benzoyl] - 4 - (2 - piperidinoethyl) - piperidine hydrochloride (m.p. 158.5—160° C.), 1 - [4 - (2 - phenoxyethoxy) - benzoyl] - 4 - (2 - piperidinoethyl) - piperidine (m.p. 103—106° C.), 1 - [4 - (2 - n - butylthioethoxy) - benzoyl] - 4 - (2 - piperidinoethyl) - piperidine hydrochloride (m.p. 161—163° C.), 1 - (4 - n - heptylbenzoyl) - 4 - (2 - piperidinoethyl) - piperidine hydrochloride (m.p. 173—173.5° C.), and 1 (4 - n - octylbenzoyl) - 4 - (2 - piperidinoethyl) - piperidine hydrochloride (m.p. 177—179° C.), were obtained.

EXAMPLE 7

By substituting in the procedure described in the Example 5 above equimolar amounts of 4 - piperidinomethyl - piperidine dihydrochloride, 4 - (3 - piperidinopropyl) - piperidine dihydrochloride, 4 - (2 - N - methylcyclohexylaminoethyl)piperidine dihydrochloride, 4 - (2 - morpholinoethyl) - piperidine dihydrochloride, 3 - (piperidinomethyl) - piperidine dihydrochoride, 4 - (2 - pyrrolidinoethyl) - piperidine dihydrochloride, 4 - (2 - hexamethyleneimineethyl) - piperidine dihydrochloride, 4 - [2 - (3 - methylpiperidino) - ethyl] - piperidine dihydrochloride, or 4 - [2 - (4 - methylpiperidino) - ethyl] - piperidine hydrochloride, for the 4 - (2 - piperidinoethyl) - piperidine dihydrochloride, 1 - (4 - n - hexyloxybenzoyl) - 4 - piperidinomethyl piperidine hydrochloride (m.p. 199—200.5° C.). 1 - (4 - n - hexyloxybenzoyl) - 4 - (3 - piperidinopropyl) - piperidine hydrochloride (m.p. 147—149° C.),

1 - (4 - n - hexyloxybenzoyl) - 4 - (2 - N - methylcyclohexylaminoethyl) - piperidine hydrochloride (m.p. 194—195° C.), 1 - (4 - n - hexyloxybenzoyl) - 4 - (2 - morpholinoethyl) - piperidine hydrochloride (m.p. 185.5—187° C.), 1 - (4 - n - hexyloxybenzoyl - 3 - (piperidinomethyl) - piperidine hydrochloride (m.p. 149—151° C.),

1 - (4 - n - hexyloxybenzoyl) - 4 - (2 - pyrrolodinethyl) - piperidine hydrochloride (m.p. 142.5—144.5° C.), 1 - (4 - n - hexyloxybenzoyl) - 4 - (2 - hexamethyleneimino-ethyl) - piperidine hydrochloride (m.p. 166.5—168.5° C.), 1 - (4 - n - hexyloxybenzoyl) - 4 - [2 - (3 - methylpiperidino) - ethyl] - piperidine hydrochloride (m.p. 174.5—177° C.), and 1 - (4 - n - hexyloxybenzoyl) - 4 - [2 - (4 - methyl - piperidino) - ethyl] - piperidine hydrochloride (m.p. 178—180° C.) were obtained.

EXAMPLE 8

By using in the procedure described in the Example 5 above and substituting equimolar amounts of 4 - n - amyloxybenzoyl chloride for the 4 - n - hexyloxybenzoyl chloride and 48% hydrobromic acid for the ethanolic hydrochloric acid, 1 - (4 - n - amyloxybenzoyl) - 4 - (2 - piperidinoethyl) - piperidine hydrobromide (m.p. 192.5—194° C.) was obtained.

EXAMPLE 9

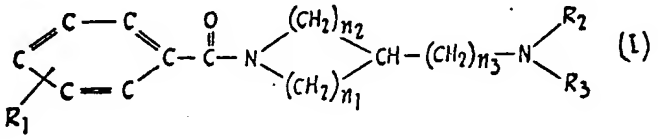
Tablets containing 5 mg. of the active compound, and the following composition, were prepared as described below:

1 - (4 - n - hexyloxybenzoyl) - 4 - (piperidinoethyl) - piperidine, hydrochloride	5 mg.
Lactose	69 mg.
Starch	57 mg.
Gelatone	2 mg.
Talc	9 mg.

The calculated amount of active compound, lactose, and starch, were mixed, granulated with a solution of gelatine in water and dried. After sifting the calculated amount of talc is added, the tablets are made by means of a 17 mm. punching die which provides tablets weighing 142 mg. each corresponding to 5 mg. of the active compound per tablet.

WHAT WE CLAIM IS:—

1. A compound of the general formula (I)



(I)

wherein R_1 is a straight or branched C3 to C12 aliphatic hydrocarbon chain, unsubstituted or substituted with phenyl, phenoxy or phenylthio, which R_1 is directly attached to the benzene nucleus, or optionally may be attached to the benzene nucleus through a hetero atom which is an oxygen or sulphur atom; R_2 is alkyl; R_3 is a cycloalkyl radical with from 5 to 8 carbon atoms in the ring, and R_2 together with R_3 can complete a heterocyclic ring which may be alkyl-substituted, n_1 is an integer from 2 to 4, n_2 is an integer from 1 to 5, and n_3 is an integer from 1 to 3; or a salt of the compound with a pharmaceutically acceptable inorganic or organic acid.

2. A compound according to Claim 1 in which n_3 is 2 or 3, and R_1 is attached to the nucleus at the 4-position.

3. A compound according to Claims 1 and 2 in which n_1 and n_2 have the value 2, and R_1 is a C5/to C7 aliphatic hydrocarbon chain attached to the benzene nucleus through the hetero atom 0.

4. A compound according to claims 1, 2 and 3 in which R_2 and R_3 form part of a heterocyclic ring.

5. A compound as claimed in claim 4, in which R_2 and R_3 form part of a heterocyclic ring selected from the group consisting of the pyrrolidino, the piperidino, the hexamethylenimino, and the heptamethylenimino rings.

6. A compound as claimed in claim 5 in

which R_1 is the n-pentyl or the n-hexyl group.

7. 1 - [4 - (3 - phenylpropoxy) - benzoyl] - 4 - (2 - piperidinoethyl) - piperidine and salts thereof.

8. 1 - [4 - (2 - phenoxyethoxy) - benzoyl] - 4 - (2 - piperidinoethyl) - piperidine and salts thereof.

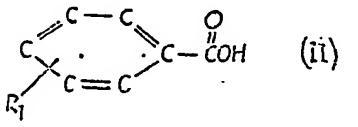
9. 1 - (4 - n - hexyloxybenzoyl) - 4 - (2 - hexamethyleneiminoethyl) - piperidine and salts thereof.

10. 1 - (4 - n - hexyloxybenozyl) - 4 - [2 - (4 - methylpiperidino) - ethyl] - piperidine and salts thereof.

11. 1 - (4 - n - amyloxybenzoyl) - 4 - (2 - piperidinoethyl) - piperidine and salts thereof.

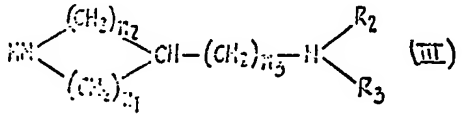
12. 1 - (4 - n - hexyloxybenzoyl) - 4 - (piperidinoethyl) - piperidine and salts thereof.

13. A method of producing a compound of the general formula I as claimed in Claim 1 wherein an acid of the general formula (II)



(II)

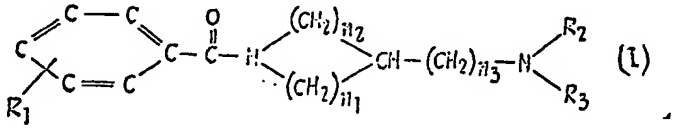
in which R_1 has the meaning herinbefore defined is reacted in the form on an acid halide, an anhydride, a mixed anhydride with an alkyl-carbonic acid, a carboxylic acid, a sulphonic acid or with an inorganic acid, or in the form of a reactive derivative obtained by reacting the acid with a carbodiimide or N',N' - carbonyldiimidazole, with a compound of the general formula:



(III)

in which R_2, R_3, n_1, n_2 and n_3 have the meanings hereinbefore defined, whereafter the compound formed is recovered as such or as one of its salts with acids.

14. A pharmaceutical preparation in dosage unit form for the treatment of patients suffering from parkinsonism comprising as at least one active component a compound of the general formula I



(I)

wherein R_1 is a straight or branched C4 to C12 aliphatic hydrocarbon chain, unsubstituted or substituted with phenyl, phenoxy or phenylthio, which R_1 is directly attached to the benzene nucleus, or optionally may be attached to the benzene nucelus through a hetero atom which is an oxygen or sulphur atom; R_2 is alkyl; R_3 is a cycloalkyl radical with from 5 to 8 carbon atoms in the ring, and R_2 together with R_3 can complete a heterocyclic ring which may be alkyl-substituted, n_1 is an integer from 2 to 4, n_2 is an integer from 1 to 5, and n_3 is an integer from 1 to 3; and its salts with pharmaceutically acceptable inorganic and organic acids together with an atoxic pharmaceutically acceptable carrier, the quantity of the said compound of formula I in the unit being between 0.1 and 50 mg. calculated as the free base.

15. A pharmaceutical preparation in oral dosage unit form as claimed in claim 14, in which the units contain from 0.5 to 25 mg. of 1 - (4 - n - hexyloxybenozyl) - 4 - (2 - piperidinoethyl) - piperidine.

16. A pharmaceutical preparation in dosage form as claimed in claim 14 or 15, in which the units contain from 1 to 10 mg. of 1 - (4 - n - hexyloxybenzoyl) - 4 - (2 - piperidinoethyl) - piperidine.

17. A pharmaceutical preparation in dosage unit form as claimed in any one of Claims 14 to 16, in the form of pills, tablets or capsules.

18. A pharmaceutical preparation in dosage unit form as claimed in Claim 14, in which the preparation is an injectable preparation containing from 0.1 to 25 mg. of the compound of formula I.

19. A pharmaceutical preparation in dosage unit form as claimed in Claim 18, in which the active ingredient is 1 - (4 - n - hexyloxybenzoyl) - 4 - (2 - piperidinoethyl) - piperidine in the form of one of its salts with a non-toxic acid dissolved in an aqueous medium.

20. A compound of the general formula 1 defined in Claim 1 substantially as hereinbefore described in any one of Examples 1 to 8 of the foregoing Examples.

21. A method of producing a compound of the general formula I defined in Claim 1 substantially as hereinbefore described in any

one of Examples 1 to 8 of the foregoing Examples.

22. A pharmaceutical preparation in dosage unit form substantially as hereinbefore described in Example 9 of the foregoing Examples.

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